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ON MECHANISM OF ADVERSE REACTIONS CAUSED BY INTRAVENOUS ADMINISTRATION OF FAT EMULSION

by

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I. INTRODUCTION

Since HIKASA (1949) succeeded in production of a fat emulsion which could be administered intravenously, his coworkers in our laboratory have clarified the metabolic process of the infused fat emulsion by means of experimental studies and have established that the fat emulsion is satisfactory for parenteral nutriment. In clinical application, however, we had great trouble. The fat emulsion, which although can be safely infused experimentally into animals, caused adverse reactions occasionally, such as chill, pyrexia, lumbago, flushing of face and agony in the breast.

The author reexamined the fat emulsion itself fundamentally and performed experimental studies to clarify the mechanism of these adverse reactions. The present paper reports these results.

II. EXPERIMENTAL MATERIALS USED AND METHODS EMPLOYED

1. Experimental Materials Used.

A) *Fat Emulsion* : Cod liver oil emulsion, sesame oil emulsion, the fat emulsion which was produced by means of molecular distillation, and synthesized fat emulsion were used.

B) *Used Drugs* : *l*-methionine, riboflavin-5'-phosphate, *l*-ascorbic acid, niacin amide, thiamin hydrochloride and 3-5-3'-4'-pentaoxy-flavon-3-ramunoglycoside (Vitamin P) were used in the form of solution.

C) *Experimented Animals* : Healthy rabbits, each weighing approximately 2.0 ~ 2.5kg, were chiefly used. In case of necessity cats and dogs were used. The animals, in whose liver parasites were found, were excluded from the experiment.

2. Experimental Methods.

A) *Extirpation of Organs* : The animals were sacrificed by bleeding without anesthesia. The organs were removed as promptly as possible.

B) *Fixation of the Organs* : The removed organs were promptly fixed in 10 per cent neutral formaldehyde solution or BAKER's solution.

C) *Embedding* : Paraffin - or carbowax-embedding was made. In case of necessity freezing method was performed.

D) *Staining Methods* : In the present study GOLDMAN's Sudan III method, SMITH-DIETRICH's method, BAKER's acid hematin method, hematoxylin-eosin method,

MAY-GIEMSA's method, DERS-STIEDA's method for hemosiderin were employed.

E) *Provocation of Hepatic Disturbance* : Rabbits were injected intramuscularly with pure carbon tetrachloride at a rate of 0.2cc per kg of body weight.

F) *Experiment during Low Diet Feeding* : The Rabbits, which had been previously fed with a standard diet (80g of wheat bran and 150g of radish leaves) for approximately 3 weeks, began to be fed with a low protein, low calorie diet (27g of wheat bran, 75g of radish leaves and adequate amount of water), at the same time daily infusion of sesame oil emulsion was started. During the first 10 days of the experiment the fat emulsion was infused at a rate of 0.5g of fat per kg of body weight, per day, and during the last 10 days was infused at a rate of 1.0g of fat per kg of body weight, per day.

G) *Experiment in Plasmapheresis* : The rabbits, which had been previously fed with a standard diet, began to be fed with 50g of okara, 200g of hakusai leaves and 12g of starch, at the same time plasmapheresis was performed. Thus prepared hypoproteinemic rabbits were repeatedly infused with sesame oil emulsion at a rate of 0.5g of fat per kg of body weight, per day, for 15 days.

III. EXPERIMENTAL RESULTS

1. On Histological Changes in the Omentum Following Intravenous Administration of the Fat Emulsion.

Stabilizers are essential to prepare a stable fat emulsion. Protein, alkali aluminate, cholate, soap and arabic gum are usually being used as stabilizers. However, these substances could not be used in our fat emulsion because of their toxicity and low stabilizing effect. According to the rapid progress made in colloid chemistry, various kinds of stabilizers have been produced. McKIBBIN and SHAFIROFF have attempted parenteral nutrition with a fat emulsion in which Knox-20, soybean phosphatide, Demal-14, Span and Tween have been chiefly used as stabilizers. Independently we used these kinds of stabilizers in the fat emulsion in our earlier studies, and found that sorbitan monostearate and polyoxyalkylen sorbitan monostearate were satisfactory with respect of stability. Even these earlier fat emulsions were nutritiously effective in experimental animals. On the other hand, above mentioned adverse reactions occasionally appeared in the clinical application. What is the mechanism of these adverse reactions? The author examined on histological changes of tissues following intravenous administration of the fat emulsion as the first step for the purpose of enlightenment of this problem.

MILLER previously indicated that numerous plasma cells appeared in the omentum following frequent and generous intraperitoneal injection of protein fraction of tuberculous bacillus. AMANO reported similar results by means of injection of horse serum and demonstrated that these plasma cells were transformed from disturbed adventitia cells. Rabbits, which were repeatedly infused with the fat emulsion for 4 weeks, at a rate of 0.5g of fat per kg of body weight, per day, were sacrificed by bleeding. Extension preparation of the omentum was stained by GIEMSA's method, and was examined microscopically. Plasma cells markedly appeared in the

omentum, similarly to AMANO's results (Fig. 1). This is undesirable from histological view-point. Accordingly we had to improve the fat emulsion for which sorbitan monostearate and polyoxyalkylen sorbitan monostearate were used as stabilizers. However, plasma cells disappeared markedly in case of simultaneous use of Vitamin P even with this fat emulsion (Fig. 2). Since WILSON and MORTAROTTI (1947) reported a remarkable restraining activity of flavon derivatives against histamin shock in guinea pig, RAIMAN, LATER, MOSS and BEILER successively advocated antianaphylactic effect of Vitamin P. Consequently stabilizers in the fat emulsion should be reexamined fundamentally. By use of new powerful stabilizers the author succeeded in production of a new sesame oil emulsion which satisfied these conditions and the problem on hemolysis. After repeated daily infusion of this new prepared fat emulsion into rabbits, plasma cells did not appear in the omentum (Fig. 3). It was found that the stabilizers used and sesame oil itself do not have any action by which plasma cells appear in the omentum.

2. Examination on Hemolysis.

Not only the earlier cod liver oil emulsion but also sesame oil emulsion occasionally caused adverse reactions such as chill, pyrexia and lumbago etc. It was characteristic that relatively many cases experienced a lumbago. The author presumed that these adverse reactions of the fat emulsion would be caused by hemolysis which occurred by fatty acids contained in the fat emulsion, because these adverse reactions were similar to those following transfusion of stored blood. It is generally accepted that lower fatty acids (less than C_6) are soluble in water at various rate, e. g. caproic acid is soluble in water in 0.6 per cent 15 C. Solubility in water decreases promptly as number of carbon atom increases. Saturated fatty acids more than lauric acid are insoluble in water. According to results of these *in vitro* studies, it is assumed that lower fatty acids dissolved in the blood caused injury to the erythrocytes. The author examined *in vivo* this fact. After daily infusion of cod liver oil emulsion into rabbits for 4 weeks at a rate of 0.5g of fat per kg of body weight, per day, hemosiderin markedly deposited in the spleen. This result indicates that hemolysis occurred by intravenous administration of cod liver oil emulsion. The author examined on the interrelation between kinds of fatty acids contained in various fat emulsions and amount of hemosiderin in the spleen.

As generally accepted coconut oil contains not only lower fatty acids, such as caproic acid and caprylic acid, but also higher fatty acid, such as lauric acid, myristic acid, palmitic acid and stearic acid, and higher unsaturated fatty acids, such as oleic acid, linoleic acid. As analytic data of coconut oil has been evident, the author performed molecular distillation of coconut oil and prepared two kinds of fat emulsion; one contained less than C_{10} fatty acids, the other contained more than C_{12} fatty acids. These two fat emulsions were repeatedly infused into different rabbits. Hemosiderin deposit in the spleen was slightly observed in the latter fat emulsion, on the contrary in the former fat emulsion, it was observed markedly. Furthermore when the rabbits were repeatedly infused with the fat emulsion pro-

duced by triglycerides of synthetized palmitic acid, oleic acid and stearic acid, hemosiderin deposit was slightly observed, similar to that after infusion of the fat emulsion which contained higher fatty acids produced by means of molecular distillation. This fact indicates that results of *in vitro* experiment agree with those *in vivo*. Therefore it is not desirable to infuse the cod liver oil emulsion containing lower fatty acid in large quantity.

The author furthermore re-examined on various kinds of natural oil and reached the conclusion that sesame oil emulsion would be the most satisfactory materials for fat emulsion. Because sesame oil did not contain any lower fatty acids as shown in Table 1.

Moreover it has been recognized

Table 1

Analysis-table of Fatty Acids in Sesame Oil

Fatty acids	Per cent
Linoleic acid	44.7
Oleic acid	34.5
Saturated fatty acids (Palmitic acid) (Stearic acid)	21.5

that fat, which follows into the blood stream through the thoracic duct following oral intake of fat, chiefly contains higher fatty acids. On the other hand the greater part of lower fatty acids is absorbed through the portal vein to be disposed in the liver. Consequently, if we attempt to infuse fat as emulsified form into the blood stream, it is most suitable to produce fat emulsion from triglycerides of higher fatty acids only. After repeated infusion of sesame oil emulsion into rabbits for 4 weeks, hemosiderin deposit decreased markedly, similar to the results in case of the infusion of the synthetized fat emulsion or coconut oil emulsion containing no lower fatty acids (Fig. 4). Moreover, the frequency of adverse reactions also decreased more markedly than that in case of infusion of cod liver oil emulsion, which being in parallel with decreases in hemosiderin deposit in the spleen. Hemosiderin deposit is slightly observable also in any healthy rabbits (Fig. 5), but its degree after repeated infusion of sesame oil emulsion was higher than that in the healthy rabbits. Consequently, it is an undeniable fact that hemolysis occurs to some degree, even after repeated infusion of the fat emulsion containing triglycerides of higher fatty acids only.

Does hemolysis occur also after oral intake of fat? GROSSMAN and STRUB recently demonstrated that hemolysis slightly occurred in such case, but its degree was markedly lesser than that after repeated infusion of fat emulsion. Accordingly it is desirable that hemosiderin deposit after repeated infusion of fat emulsion decreases to the degree after oral intake of fat. The author attempted to improve sesame oil emulsion for this purpose and produced the fat emulsion which could be infused for 4 weeks with normal hemosiderin deposit in the spleen such as in healthy rabbits (Fig. 6).

3. On the So-called "Colloid Shock".

In clinical application of these improved fat emulsions adverse reactions such as chill, pyrexia, flushing of face and agony in the breast were occasionally observed,

but its frequency decreased markedly. What is the mechanism of these adverse reactions? It was characteristic in the clinical application that the patients, who complained of these adverse reactions when the fat emulsion of 2 cc or 3 cc were infused, did not show these adverse reactions any more when a large quantity such as 50cc of the fat emulsion was infused again. Accordingly symptoms resembling the so-called "tachyphylaxis" occurred following infusion of the fat emulsion as well as colloid substances.

The author assumed that these adverse reactions following infusion of the fat emulsion would be anaphylactoid phenomena by means of infusion of colloid substances, and experiments were made according to the following procedures; the changes of blood pressure through the carotid artery and respiration following intravenous administration of the fat emulsion into rabbits were recorded on a kymogram directly.

As shown in Fig. 7 decrease in blood pressure and superficial respiration were observed following the first infusion without sensitizing injection. These phenomena should be considered to be similar to shock inducing by intravenous medication as established by MASAKI. He demonstrated that active substances which participated in occurrence of the shock

was liberated from the blood cells, when the fibrin, which formed network with colloid substances as nucleus, and blood cells were shaken together and consequently high active substances such as A.T.P. or I.T.P. were liberated into tissue fluid to result in anaphylactoid phenomena (Table 2). Anaphylactoid phenomena did not occur since the second injection of colloid substances, because the active substances were no more liberated from the blood cells. As the fat emulsion is a kind of colloid solution, these phenomena would possibly occur. These phenomena should be prevented in case of intravenous administration of the fat emulsion. Consequently it is considered that preliminary or simultaneous injection of anticoagulants can reduce or prevent these phenomena. In the United States heparin has been mixed in the fat emulsion. However, these adverse reactions could not be prevented completely by means of this method only. Moreover, there is a danger of profuse bleeding during operation by preoperative administration of heparin. This is the reason why fat emulsion itself should be fundamentally improved without use of heparin.

Fig. 7. Changes of Blood Pressure and Respiration Following Intravenous Administration of a Fat Emulsion (Rabbit).

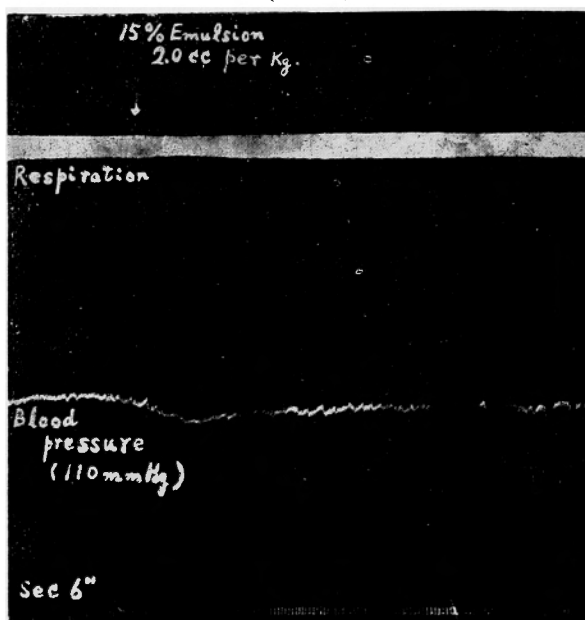


Table 2
Schema of Colloid Shock (by Masaki)

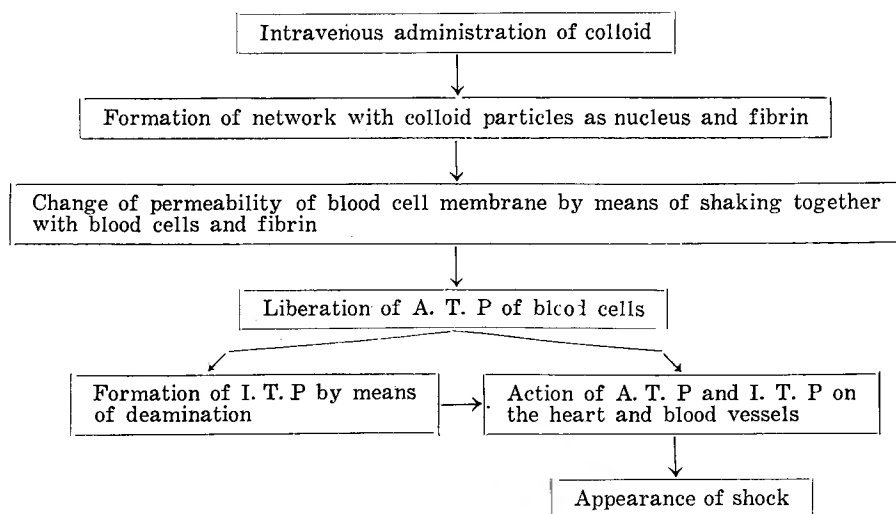


Table 3
Pyrogen Test (Rabbits)

Fat emulsion	Experimental animals	Increase in body temperature	Decision
Earlier fat emulsion	1	+ 1.50 °C	(+)
	2	+ 1.10 °C	(+)
	3	+ 1.10 °C	(+)
	4	+ 0.75 °C	(+)
	5	+ 0.60 °C	(+)
New fat emulsion	1	- 0.25 °C	(-)
	2	+ 0.20 °C	(-)
	3	+ 0.13 °C	(-)
	4	+ 0.20 °C	(-)
	5	- 0.15 °C	(-)
	6	+ 0.35 °C	(-)

The author produced sesame oil emulsion, which could be infused into rabbits without any adverse and pyrogenic reactions, by means of recent techniques (Table 3).

4. On Development of Fatty Liver Following Intravenous Administration of Fat Emulsion.

A) Intravenous Administration of the Fat Emulsion into Healthy Rabbits.

Previously ASADA reported that phospholipids accumulated markedly in the hepatic parenchymatous cells, especially in the peripheral region of the hepatic lobules, when repeated infusions of cod liver oil emulsion alone were made for three weeks, at a rate of 0.25g of fat per kg of body weight, per day, into rabbits having weak ability in fat disposal. In the present study, healthy rabbits were repeatedly infused with cod liver oil emulsion for 8, 9 or 10 weeks. In all rabbits

fatty liver developed markedly as shown in Fig. 8. When the repeated infusions of cod liver oil emulsion were made jointly with subcutaneous injection of *l*-methionine at a rate of 5mg per kg of body weight, per day, phospholipid accumulation in the hepatic parenchymatous cells and fatty liver were not observed. In other words, when cod liver oil emulsion, which contained lower fatty acids in relatively large quantity, was repeatedly infused without simultaneous use of methionine, fatty liver always developed.

On the contrary, when sesame oil emulsion, which contained higher fatty acids only was infused in double doses (0.5g of fat per kg of body weight per day), phospholipids did not accumulate in the hepatic parenchymatous cells (Fig. 9). Fig. 10 showed that fatty liver did not develop at all after 10 weeks infusion. Furthermore, even after 8 months infusion (simultaneously infused with riboflavin and *l*-ascorbic acid according to the results of HASHINO and Osa) fatty liver was not observed (Fig. 11). These results indicate that sesame oil emulsion is more satisfactory than cod liver oil emulsion for the purpose of parenteral nutrition with fat.

B) Intravenous Administration of the Fat Emulsion into Rabbits with Mal Nutrition.

Clinical objects of parenteral nutrition are poorly nourished patients e. g. hypo-proteinemic patients. GRÖRGY and GOLDBLATT reported that a low protein, low calorie diet feeding caused fatty infiltration, necrosis and cirrhosis of the liver. Is it appropriate to infuse continuously the fat emulsion into these patient? The following two experiments were performed for purpose of examining this question.

(i) *Experimental Results during Low Diet Feeding.*

Table 4
Decrease in Weight of Rabbits Fed with Low Diet.

Remarks	Weight loss (gm)	Change of body weight (%)
Without infusion	(840) *	(- 39.1) *
7% Glucose + Methionine	960	- 42.4
7% Glucose + Methionine + Riboflavin	860	- 38.5
7% Glucose + 5% Glucose(16cc) + Methionine + Riboflavin	710	- 33.5
Fat emulsion	370	- 17.5
Fat emulsion + Methionine	386	- 17.5
Fat emulsion + Methionine + Riboflavin	300	- 13.7
Fat emulsion + 5% Glucose(16cc) + Methionine + Riboflavin	173	- 8.1
Fat emulsion + 5% Glucose(16cc) + Methionine + Riboflavin + Niacin amide + Ascorbic acid + Thiamin hydrochloride.	140	- 6.6

* () Died after 15 th or 18 th of Experimental Days,

When rabbits were fed with the above mentioned low diet (the low protein, low calorie diet) without any treatment, the body weight decreased rapidly (rate of weight loss showed 39.1 per cent), resulting to death after 15th to 18th of experimental days. When repeated daily infusion of sesame oil emulsion was performed concurrently with the beginning of the low protein, low calorie diet feeding, rate of weight loss remained at 17.8 per cent on an average after 3 weeks and phospholipids hardly accumulated in the hepatic parenchymatous cells (Fig. 12) and fatty liver was not observed histologically (Fig. 13). As reported by Osa, intravenous administration of the fat emulsion was effective, showing a sparing effect of tissue protein and depot fat, and was not injurious at all. Of course, when *l*-methionine, riboflavin, *l*-ascorbic acid and niacin amide were infused simultaneously with the fat emulsion, fatty liver was not observed in all cases.

(ii) *Experimental Results in Plasmapheresis.*

Healthy rabbits began to be fed with 50g of okara, 20g of hakusai leaves and 12g of starch, at the same time plasmapheresis was carried out to decrease serum protein concentration to 4.8g/dl and to diminish the ratio of hepatic soluble protein to insoluble protein, to 1.12. These prepared hypoproteinemic rabbits were infused repeatedly with sesame oil emulsion for 3 weeks at a rate of 0.5g of fat per kg of body weight, per day, concurrently with beginning of feeding with 300g of okara (in this experiment 2.5mg of riboflavin, 5mg of niacin amide and 10mg of *l*-ascorbic acid per kg of body weight were infused simultaneously with the fat emulsion). Accumulation of phospholipids in the hepatic parenchymatous cells and fatty liver were not observed (Fig. 14). The above experimental results indicate that the sesame oil emulsion could be repeatedly infused into the hypoproteinemic rabbits for at least 3 weeks without development of histological fatty liver.

C) Intravenous Administration of the Fat Emulsion into the Rabbits with Hepatic Disturbance Caused by Carbon Tetrachloride.

The above results demonstrate that the fat emulsion was safely infused even into the rabbits with hepatic disturbance produced by the low protein, low calorie diet feeding. Can the fat emulsion be infused into the rabbits with more intensive hepatic disturbance? Hepatic disturbance can be produced by means of a low protein, low calorie diet feeding, or ligation of the hepatic artery, or ligation of the biliary tract, or partial hepatectomy, or toxication with carbon tetrachloride or chloroform or phosphorus, but in this experiment, carbon tetrachloride was used.

Rabbits were previously divided in five groups and were intramuscularly injected with 0.1cc to 0.5cc of carbon tetrachloride per kg of body weight. Histological findings of the liver after 24 hours are shown in Table 5 and Fig. 15. As the greater part of the rabbits in the groups of more than 0.3cc injection died, the groups of less than 0.2cc injection were repeatedly infused with sesame oil emulsion. In this experiment 5mg of *l*-methionine, 3mg of riboflavin and 10mg of *l*-ascorbic acid per kg of body weight were infused simultaneously with the fat emulsion. After 4 week infusion, KUPFFER's stellate cells phagocytized fat globules and hypertrophied, and destruction of the hepatic cells had been almost restored, and vacuo-

Table 5
Histological Findings in the Liver 24 Hours after Injection
of Carbon Tetrachloride

Doses of CCl ₄	Arrangement of cellular tract	Vacuolization	Disappearance of nucleus	Deformation and destruction of cells	Deposition of fat
0.1 cc	relatively irregular	±	-	-	++
0.2 cc	irregular	++	+	+	++
0.3 cc	irregular	++	+	++	++
0.4 cc	irregular	+++	++	+++ Destruction and vacuolization in central region	++
0.5 cc	irregular	+++	++	+++ in central and intermediary region	++

lization in the cells had almost disappeared. In other words, when the fat emulsion was infused simultaneously with methionine and various vitamins which were concerned with fat metabolism into the rabbits with hepatic disturbance, fatty liver could not be promoted (Fig. 16).

IV. DISCUSSION

There are two main methods for parenteral nutrition with fat. One is intravenous administration of fatty acids as the form of soap, and the other is intravenous administration of emulsified fat. According to partition theory on intestinal fat absorption, the latter method is more physiological, on the other hand, the former is non-physiological. We have applied the latter method and have studied the metabolic process of the infused fat emulsion. In case of parenteral nutrition with fat emulsion there are the following problems.

- (1) histological changes of tissues.
- (2) hemolysis.
- (3) colloid shock.
- (4) development of fatty liver.

The author investigated, by means of experimental studies, these four problems, and attempted to remove all adverse reactions of the fat emulsion. Namely, various kinds of stabilizers which were necessary to produce fat emulsion were examined with respect of histological changes, according to AMANO's and MILLER's results. New stabilizers, which answered to our purpose were found, and that sesame oil was found to be the most satisfactory materials of fat emulsion. Furthermore, the relationship between kinds of fatty acids and hemolysis was examined *in vivo* and it was recognized that results *in vivo* agreed with those *in vitro*. These results demonstrate that esters of lower fatty acids, especially the oil which contained triglycerides of lower fatty acids in relatively large quantity, should be avoided to be used as materials of fat emulsion. Lower fatty acids are not meta-

bolized smoothly as indicated by OSA and IZUKURA, and it was established that their repeated infusion caused fatty liver. On the other hand, repeated infusion of sesame oil emulsion contained only triglycerides of higher fatty acids, caused hemolysis to some degree. Precautions against these phenomena were studied and the author succeeded in production of a new fat emulsion which could be infused safely.

It has been demonstrated from our laboratory that the infused fat globules are first phagocytized by the reticuloendothelial cells and are changed to phospholipids. In case of infusion of cod liver oil emulsion which contained triglycerides of lower fatty acids in relatively large quantity, phospholipids appeared in the hepatic parenchymatous cells in large quantity. On the contrary, in case of sesame oil emulsion which contained triglycerides of higher fatty acids only, it was observed in very small quantity. These results established histologically that lower fatty acids are always utilized only in the hepatic parenchymatous cells, and contrarily, higher fatty acids are metabolized not only in the liver but also in extrahepatic tissue cells. Repeated excessive infusions of triglycerides of lower fatty acids are a burden on the liver, resulting in development of fatty liver. Consequently it is rational that the fat emulsion which contained triglycerides of higher fatty acids only, being easily utilized, such as sesame oil emulsion, is infused for the purpose of parenteral nutrition. However, when even cod liver oil emulsion was infused simultaneously with methionine, accumulation of phospholipids in the hepatic parenchymatous cells and fatty liver did not appear. From this result, it would be considered that methionine accelerates not only lipoidization of neutral fat in the reticuloendothelial cells but also fatty acid oxidation in the hepatic parenchymatous cells, as reported by ENTENMAN, ARTOM and HASHINO.

It has been demonstrated that sesame oil emulsion is able to be safely and repeatedly infused into the hypoproteinemic rabbits produced by plasmapheresis or the low diet feeding rabbits or the hypoproteinemic patients without any abnormal histological findings. It is of course desirable in respect of a sparing effect of protein and depot fat that ascorbic acid, riboflavin, niacin amide and pantothenic acid are used simultaneously with the fat emulsion. Nutritional effect of the fat emulsion is also doubled by means of simultaneous use of adequate amount of thiamin and glucose. In case of hepatic disturbance further simultaneous use of methionine is essential.

Thus these three problems were experimentally solved. Consequently, the adverse reactions disappeared markedly when sesame oil emulsion was used, in contrast to cod liver oil emulsion. However, even this improved sesame oil emulsion caused occasionally adverse reactions such as chill, pyrexia, flushing of face and agony in the breast. According to the results of the present study the author concluded that these adverse reactions were caused by anaphlactoid phenomena by means of intravenous administration of fat emulsion viz. colloid substance. Mixture of heparin in fat emulsion is one of the precautions, but this method is undesirable in practice, as mentioned before. The author succeeded in production of the fat

emulsion which is relatively safe from these dangers and is non-pyrogenic.

V. CONCLUSION

The author studied experimentally on the mechanism of adverse reactions in clinical application of the earlier fat emulsion, and reached the following conclusions.

(1) When colloid substances, such as fat emulsion, are administered intravenously, the following four problems must be examined; hemolysis, colloid shock, histological changes of tissues and fatty liver.

(2) As triglycerides of lower fatty acids caused remarkable hemolysis also *in vivo*, these substances should be avoided as much as possible in case of parenteral nutrition with fat emulsion.

(3) Use of sorbitan monostearate and polyoxyalkylen sorbitan monostearate was not desirable with respect of histological changes of tissues.

(4) Infusion of colloid substances such as fat emulsion, definitely caused colloid shock, if the precautions were not taken.

(5) Repeated infusion of the fat emulsion which contained triglycerides of lower fatty acids in large quantity, caused development of fatty liver. On the contrary, there was no possibility of this danger in case of infusion of the fat emulsion which contained triglycerides of higher fatty acids only.

(6) This improved fat emulsion could be administered intravenously even into human being without any adverse reactions mentioned above.

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(和文抄録)

経静脈性脂肪輸入時の副作用発現機序に関する実験的研究

京都大学医学部外科学教室第2講座(指導:青柳安誠教授)
東洋レーヨン株式会社滋賀工場附属病院外科(院長:立川律三)

研 究 生 大 谷 誠 二

何等原料脂質, 安定剤等を顧慮することなく作成した脂肪乳剤を, 人体静脈内へ注入する時は, 著しい副作用を招来するが, 本実験に於てはその理由を実験的に究明すると共に, また防止対策をも究明して次の結論に到達した。

(1) 脂肪乳剤のような一種のコロイド物質を直接静脈内へ注入するに当つては, その注入によつて溶血現象, 組織反応, コロイド・ショック, 脂肪肝等が惹起されるかどうか予め充分検討しておく必要がある。

(2) 低級脂肪酸の Triglyceride は, 乳剤として静脈内へ注入すると著しい溶血現象を呈するのみならず, 之を長期に亘り反覆注入すれば, 脂肪肝発生の恐れがある。

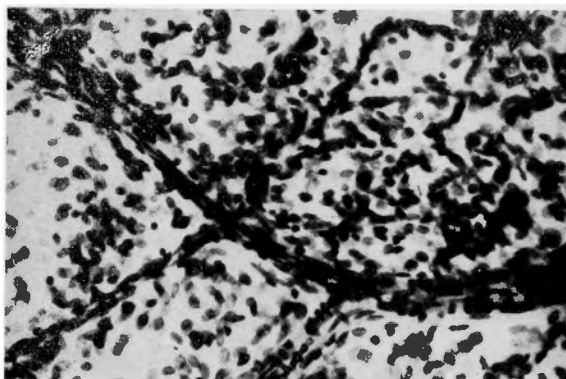
(3) 高級脂肪酸の Triglyceride のみからなる脂肪乳剤は, 之を反覆注入しても脂肪肝を惹起しない。併し特別の対策を講ぜざる限り, なお多少共溶血現象, コロイド・ショックは発現する。

(4) 以上の点から我々は脂肪乳剤の原料として高級脂肪酸の Triglyceride のみからなる精製胡麻油を使用するに至つたが, 肝油のような低級脂肪酸の Triglyceride を含む脂肪は, 使用しない方がよい。

(5) 我々が使用している精製胡麻油は, 組織反応の面からも充分静脈内注入用脂肪乳剤の原料として使用に耐え得る。又斯る観点から安定剤に就ても検討し, その目的に合致する強力な而も無害な安定剤を見出すに至つた。

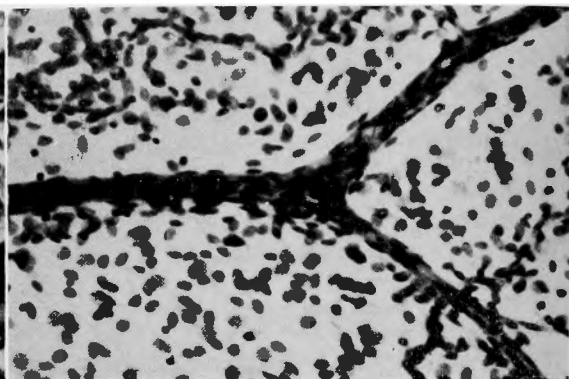
(6) 従つて我々の新たに作製した胡麻油乳剤を使用しても溶血現象, 組織反応, 脂肪肝等の発生する危険は全くない。

(7) その静脈内注入に際して必然的に惹起されるコロイド・ショックも, 動物実験的には可及的軽減せしめることができた。そしてまた人体静脈内注入も安全に施行し得た。



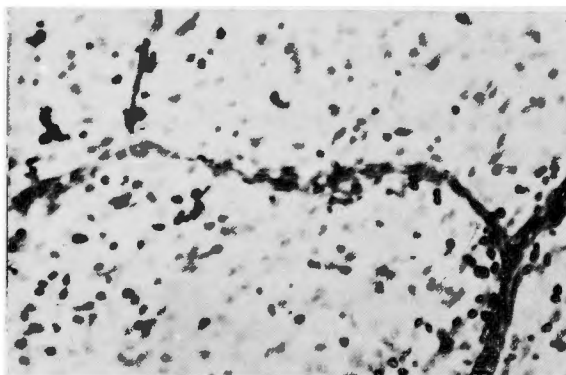
×200. (May-Giemsa.)

Fig. 1. Plasma cells in the omentum after intravenous administration of the fat emulsion which contains sorbitan monostearate and polyoxyalkylen sorbitan monostearate.



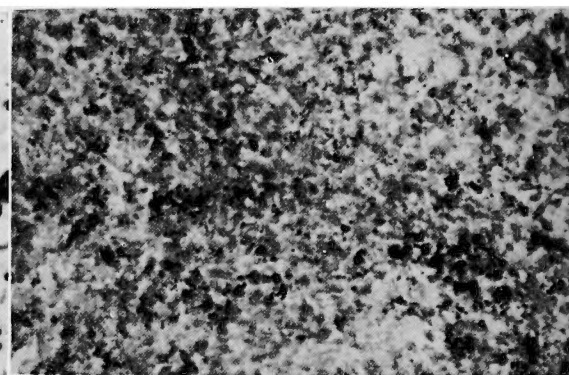
×200. (May-Giemsa)

Fig. 2. Plasma cells in the omentum after simultaneous infusion of Vitamin P with the fat emulsion which contains sorbitan monostearate and polyoxyalkylen sorbitan monostearate.



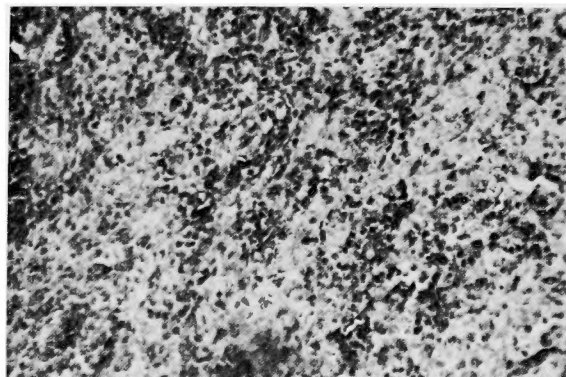
×200. (May-Giemsa)

Fig. 3. Omentum stained by Giemsa's method after intravenous infusion of a new prepared fat emulsion (Plasma cells did not appear).



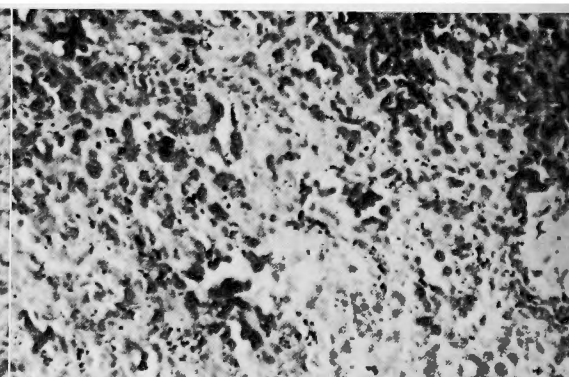
×500. (H. E.)

Fig. 4. Hemosiderin in the spleen after 4 week infusion of sesame oil emulsion.



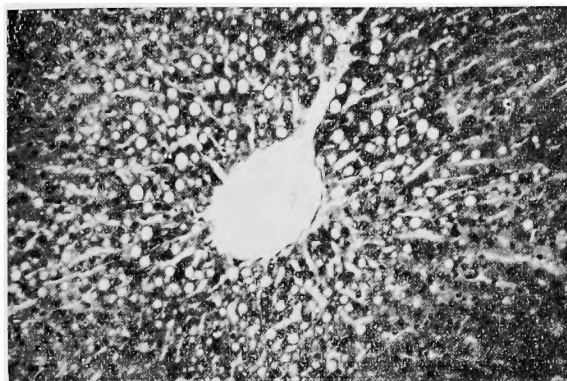
×500. (H. E.)

Fig. 5. Hemosiderin in the spleen of healthy rabbit.



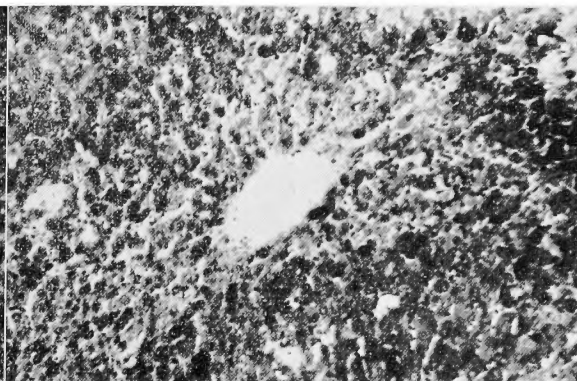
×500. (H. E.)

Fig. 6. Hemosiderin in the spleen after 4 week infusion of a new prepared fat emulsion.



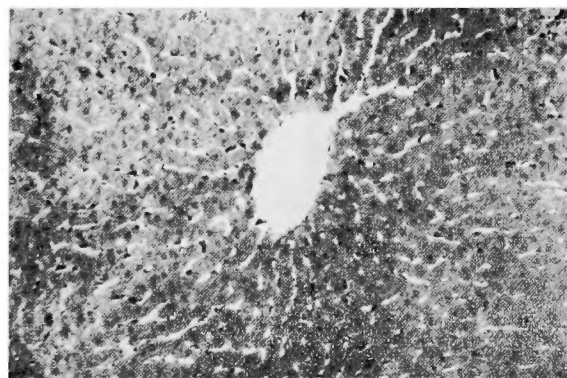
×150. (Sudan III)

Fig. 8. Fatty liver occurred by 10 week infusion of cod liver oil emulsion.



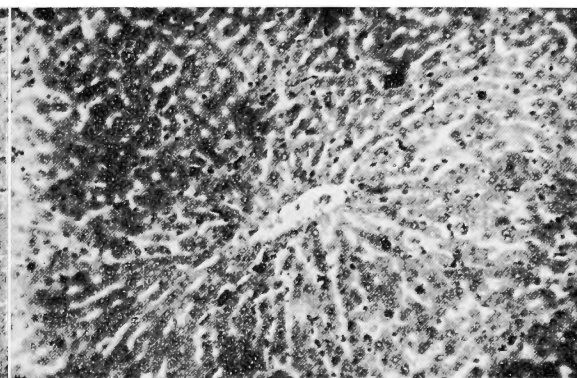
×150. (Smith-Dietrich)

Fig. 9. Phospholipid in the liver after 10 week infusion of sesame oil emulsion.



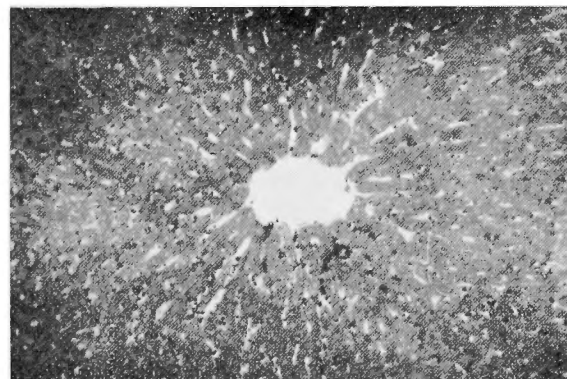
×150. (Sudan III)

Fig. 10. Liver after 10 week infusion of sesame oil emulsion.



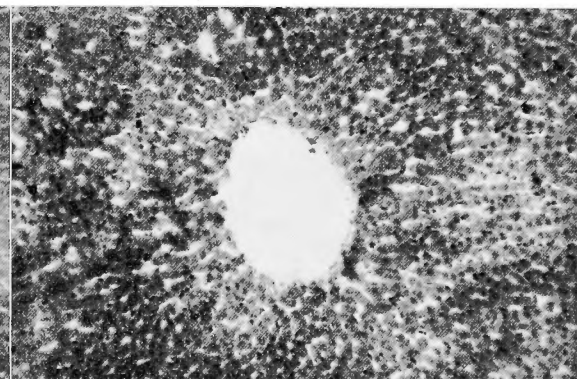
×150. (Sudan III)

Fig. 11. Liver after 8 month infusion of sesame oil emulsion.



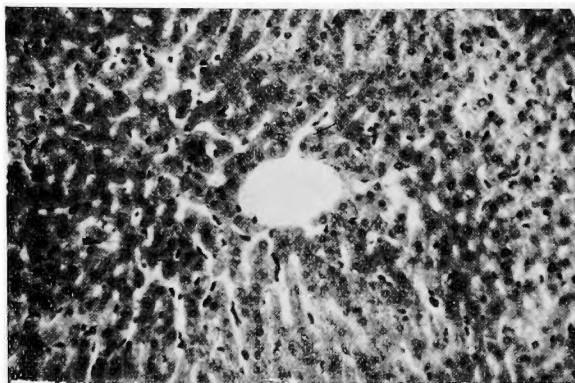
×150. (Smith-Dietrich)

Fig. 12. Phospholipid in the liver after 3 week infusion of sesame oil emulsion alone into the rabbit fed with a low diet.



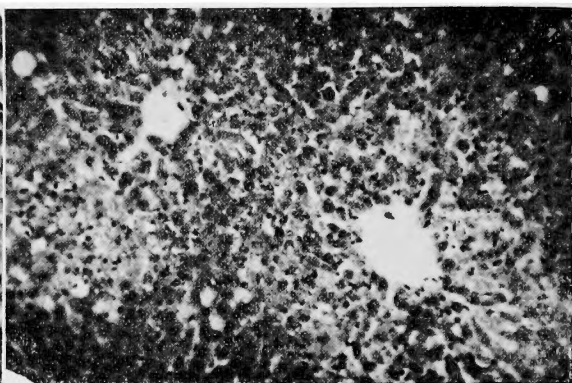
×150. (Sudan III)

Fig. 13. Liver after 3 week infusion of sesame oil emulsion alone into the rabbit fed with a low diet.



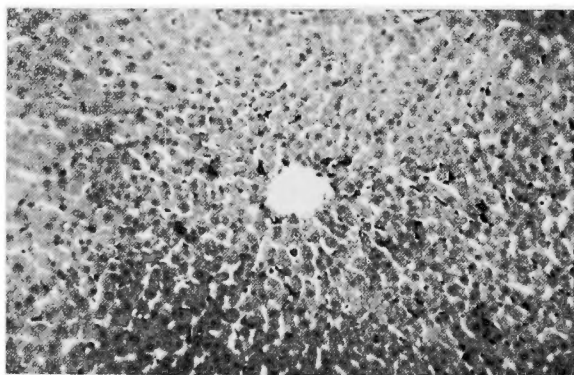
×150. (Sudan III)

Fig. 14. Liver after 3 week simultaneous infusion of vitamins with the sesame oil emulsion into the hypoproteinemic rabbit produced by plasmapheresis.



×150. (Sudan III)

Fig. 15. Fatty liver 24 hours after injection of carbon tetrachloride (0.2cc per kg of body weight).



×150. (Sudan III)

Fig. 16 Liver after 3 week simultaneous infusion of methionine and vitamins with the sesame oil emulsion into the rabbit with hepatic disturbance caused by injection of carbon tetrachloride.